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REMARKS

Upon entry of this amendment, claims 1-5, 7, 12-19, 21 and 26-28 are pending in the instant application. Claims 1-5, 7, 12-19, 21, and 26-28 have been amended herein, and claims 6, 8-11, 20 and 22-25 have been cancelled without prejudice or disclaimer. Applicants reserve the right to prosecute that subject matter, as well as the originally presented claims, in continuing applications. Support for the claim amendments presented herein can be found throughout the specification and in the claims as originally filed. For example, support for the aptazymes comprising a regulatable Group I intron and an aptamer oligonucleotide, as recited by amended claims 1 and 15 (and their respective dependent claims) is found at least at page 30, line 17 through page 31, line 5; at page 31, lines 18-22; at page 38, lines 1-16; at page 39, line 1 through page 40, line 2. Accordingly, no new matter has been added by these amendments.

I. Oath/Declaration

The Examiner has asserted that the Declaration is defective because "the Declaration does not acknowledge the filing of the provisional application for which the instant application claims benefit."

Applicants traverse this objection. On November 16, 2001, Applicants' previous representatives filed a Declaration executed by each of the named inventors of this application (*i.e.*, Andrew D. Ellington, Michael P. Robertson, and Kristen A. Marshall). Applicants contend that this Declaration filed on November 16, 2001 is fully compliant with the requirements under 37 C.F.R. §§ 1.63-64. A courtesy copy of the November 16, 2001 Declaration is attached hereto.

Contrary to the Examiner's assertion that the original Declaration does not acknowledge the provisional application to which this application claims priority, Applicants note that page 1 of the Declaration states "I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below", and the top of page 2 clearly recites the following information:

United States Provisional Application
Serial No.: 60/292,097, Filed June 15, 2000
(60/212,097) (06/15/2000)

Thus, this information listed on page 2 of the Declaration is a "United States provisional application listed below" the priority claim under 35 U.S.C. §119(e) on page 1 of the

Declaration. Applicants, therefore, contend that the November 16, 2001 Declaration does "acknowledge the filing of the provisional application for which the instant application claims benefit." Accordingly, Applicants submit that a supplemental oath or declaration pursuant to 37 C.F.R. §1.67 is unnecessary, and this objection should be withdrawn.

II. Nucleotide and/or Amino Acid Sequence Disclosure

The Examiner has asserted that the Preliminary Amendment (Paper No. 12), filed on October 22, 2002 is not fully responsive to the Notice to Comply mailed on September 21, 2002. According to the Examiner, Figures 2A, 2B and 3 "contain aptamer constructs but do not have accompanying SEQ ID numbers."

Applicants note that Figures 1, 2A, 2B and 3 have been amended herein to include sequence identifier tags (*i.e.*, SEQ ID numbers). In addition, the descriptions of these figures at page 10 of the specification have been amended to include a SEQ ID number for each nucleic acid sequence presented in Figures 1, 2A, 2B and 3. In addition, the nucleic acid sequences presented in Figures 1, 2A, 2B and 3 have been included in the Substitute Sequence Listing submitted herewith.

Applicants contend that the Substitute Sequence Listing submitted herewith, in conjunction with the amendments presented herein, place this application in compliance with the requirements set forth in 37 C.F.R. §§1.821-1.825. Accordingly, Applicants request that this objection be withdrawn.

III. Claim rejections under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1-5, 7, 12-19, 21 and 26-28 under 35 U.S.C. § 112, first paragraph for lack of written description. According to the Examiner, "the scope of the claimed invention encompasses an aptazyme construct comprising a regulatable domain Group I intron aptamer oligonucleotide having a regulatory domain [but] the specification as filed provides only a description of a Group I theophylline dependent intron aptamer construct (see Figure 1)." (Office Action, page 4). In addition, the Examiner has asserted that the specification "does not define 'aptazyme' or 'Group I intron aptamer' in such clear and concise terms to allow one skilled in the art to know how to identify the physical structure or characteristics of these terms." (Office Action, pages 4-5). The Examiner has concluded that the as-filed specification

"does not provide a sufficient number of representative species of an aptazyme construct comprising a regulatable domain Group I intron aptamer oligonucleotide sequence having a regulatory domain, which would allow one of ordinary skill in the art to predict the structures of all members of the claimed genus of compounds." (Office Action, page 6).

Applicants note that independent claims 1 and 15 (and their respective dependent claims, including 2-5, 7, 12-14, 16-19, 21 and 26-28) have been amended herein. Amended claim 1 is directed to regulatable aptazyme oligonucleotides that contain a Group I intron oligonucleotide and an aptamer oligonucleotide, wherein the kinetic parameters of the Group I intron oligonucleotide vary in response to the interaction of an allosteric effector molecule with the aptamer oligonucleotide. In addition, claim 15 has been amended to recite allosterically regulatable aptazymes having a Group I intron oligonucleotide and an aptamer oligonucleotide, wherein the kinetic parameters of the Group I intron oligonucleotide vary in response to the interaction of an allosteric effector molecule with the aptamer oligonucleotide, such that the intron splicing reaction occurs *in vitro*.

Thus, the pending claims are directed to regulatable aptazymes that include a Group I intron oligonucleotide *and* an aptamer oligonucleotide, such that the self-splicing activity of the Group I intron is regulated by the interaction between an allosteric effector molecule and the aptamer. Applicants contend that the terms "Group I intron oligonucleotide" and "aptamer oligonucleotide", as recited by the amended claims, are art-recognized terms, and moreover, the term "aptazyme" is sufficiently defined and described throughout the specification. In particular, Applicants assert that one of ordinary skill in the art would recognize that the term "Group I intron oligonucleotide" signifies a subset of self-splicing intron sequences that begin the intron-splicing reaction by binding a guanine nucleotide to the intron sequence. Furthermore, those skilled in the art would also appreciate that the term "aptamer oligonucleotide" refers to a nucleic acid which binds to a non-nucleic acid target molecule or a nucleic acid target through non-Watson-Crick base pairing. (*See e.g.*, On-line Medical Dictionary at <http://cancerweb.ncl.ac.uk/cgi-bin/omd>, "Aptamer", (October 13, 1997), attached hereto as Appendix C). In addition, the term "aptazyme" is defined throughout the specification as "an allosterically regulated ribozyme" or "an allosterically activated ribozyme" in which the activity of the ribozyme is under the allosteric control of a second portion of the ribozyme, referred to as

the "regulatory domain" (*i.e.*, the aptamer oligonucleotide) of the aptazyme. (*See e.g.*, specification at page 4, lines 2-15; and at page 52, lines 4-5).

Accordingly, Applicants believe that one skilled in the art at the time of the earliest effective filing date of the instant application (*i.e.*, June 15, 2000), would appreciate the structure and characteristics of the claimed "aptazyme" oligonucleotides having a "Group I intron oligonucleotide" and an "aptamer oligonucleotide". Applicants further contend that the as-filed specification provides sufficient description for such allosterically regulatable aptazyme oligonucleotides.

First, the as-filed specification describes regulatable aptazymes according to the claimed invention that include a Group I intron oligonucleotide and a target-specific aptamer oligonucleotide, wherein the kinetic parameters of the Group I intron-splicing reaction vary in response to the interaction between the effector and the aptamer oligonucleotide. (*See e.g.*, specification at page 31, lines 6-23 and in Example 1 at pages 32-35). As described in the as-filed specification, the Group I intron-splicing reaction occurs in the presence of the allosteric effector molecule. For example, the allosteric effector molecule can be theophylline, and the aptazyme according to the instant invention can be an anti-theophylline aptamer oligonucleotide. In these theophylline-regulated aptazyme oligonucleotides, the Group I intron-splicing reaction is regulated by the presence of theophylline. Thus, Applicants contend that the as-filed specification provides sufficient description for effector-regulated aptazyme oligonucleotides, such as an theophylline-regulated aptazyme oligonucleotide.

Second, the as-filed specification also describes *in vitro* selection methods for identifying a *variety of other* aptazyme oligonucleotides having a theophylline-regulated aptamer oligonucleotide. (*See e.g.*, specification at Example 2 at pages 35-37 and in Figures 3A-3B). For example, pools of aptazyme constructs were produced by linking a Group I intron oligonucleotide and an anti-theophylline aptamer oligonucleotide using a short randomized linking region. Positive and negative selections were used to select aptazyme constructs regulated by the presence or absence of theophylline.

Third, the as-filed specification also describes strategies and methods for using the disclosed selection methods to produce and identify aptazyme oligonucleotides that are regulated by other allosteric effector molecules, such as, for example, cGMP, cAMP and other small

molecule effectors. (*See e.g.*, specification at page 39, lines 1-13). Contrary to the Examiner's assertion, Applicants contend that the as-filed specification does *not* make a "mere statement that it [*i.e.*, another allosterically regulatable aptamer oligonucleotide] is part of the invention and reference to a potential method for isolating it". As described above, the specification describes methods and strategies that can be used to identify suitable aptamer oligonucleotides that are regulated by any desired effector molecules (*see e.g.*, specification at page 31, lines 6-23; and at page 39, lines 1-13). Then, the specification provides examples and experimental data to illustrate that these disclosed methods and strategies successfully produced theophylline-regulated aptazyme oligonucleotides (*see e.g.*, Example 1 at pages 32-35; Example 2 at pages 35-37 and in Figures 3A-3B), as well as aptazyme oligonucleotides that are regulated by other allosteric effector molecules (*see e.g.*, specification at page 39, line 14 through page 41, line 12; and Figures 4-6).

Thus, Applicants contend that the as-filed specification provides sufficient description for the genus of aptazymes recited by the amended claims presented herein, and this rejection should be withdrawn.

IV. Claim rejections under 35 U.S.C. § 112, second paragraph

The Examiner has also rejected claims 1-5, 7, 12-19, 21 and 26-28 under 35 U.S.C. §112, second paragraph as being indefinite. According to the Examiner, the terms "aptazyme" and "Group I intron aptamer" are unclear, as these terms are "not art recognized terms." (Office Action, page 6). The Examiner has asserted that, without a specific definition in the application, one of ordinary skill in the art would not be able to ascertain the scope of the pending claims.

Applicants note that all references to the term "Group I intron aptamer" have been removed from the pending claims. As described above, claim 1 has been amended herein to recite regulatable aptazyme oligonucleotides that contain a Group I intron oligonucleotide and an aptamer oligonucleotide, wherein the kinetic parameters of the Group I intron oligonucleotide vary in response to the interaction of an allosteric effector molecule with the aptamer oligonucleotide. Furthermore, claim 15 has been amended to recite allosterically regulatable aptazymes having a Group I intron oligonucleotide and an aptamer oligonucleotide, wherein the kinetic parameters of the Group I intron oligonucleotide vary in response to the interaction of an

allosteric effector molecule with the aptamer oligonucleotide, such that the intron splicing reaction occurs *in vitro*.

Thus, the pending claims are directed to regulatable aptazymes that include a Group I intron *and* an aptamer, wherein the self-splicing activity of the Group I intron is regulated by the interaction between an allosteric effector molecule and the aptamer. As described above, the term "Group I intron" is an art-recognized term for a specific group of self-splicing intron sequences that begin the intron-splicing reaction by binding a guanine nucleotide to the intron sequence. As an art-recognized term, those skilled in the art would understand the scope and characteristics of a "Group I intron" oligonucleotide. Applicants, therefore contend that the term "Group I intron oligonucleotide" is not unclear, and this rejection should be withdrawn.

In addition, Applicants traverse the Examiner's assertion that the term "aptazyme" is not properly defined in the specification. The term aptazyme is defined throughout the specification as "an allosterically regulated ribozyme" or "an allosterically activated ribozyme" in which the activity of the ribozyme is under the allosteric control of a second portion of the ribozyme, referred to as the "regulatory domain" of the aptazyme. (*See e.g.*, specification at page 4, lines 2-15; and at page 52, lines 4-5). Thus, the as-filed specification clearly defines the term aptazyme as being synonymous with the phrase "allosterically regulated ribozyme." Applicants contend that the terms "allosterically regulated" and "ribozyme" are art-recognized terms, and as such, one of ordinary skill in the art would be able to ascertain the scope of the term "aptazyme". Accordingly, Applicants request that the Examiner withdraw this rejection.

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

Reg No. 53,097

Ivor R. Elrifi, Reg. No. 39,529
Attorney for Applicant
Tel: (617) 542 6000
Fax: (617) 542 2241
Customer No. **30623**

Attachments:

– Appendix A (Replacement Sheets for Figures 1, 2a, 2b and 3)
– Appendix B (Annotated Sheets for Figures 1, 2a, 2b and 3, Showing Changes)
- Appendix C ("Aptazyme" entry from On-line Medical Dictionary at <http://cancerweb.ncl.ac.uk/cgi-bin/omd>)

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Figure 1.

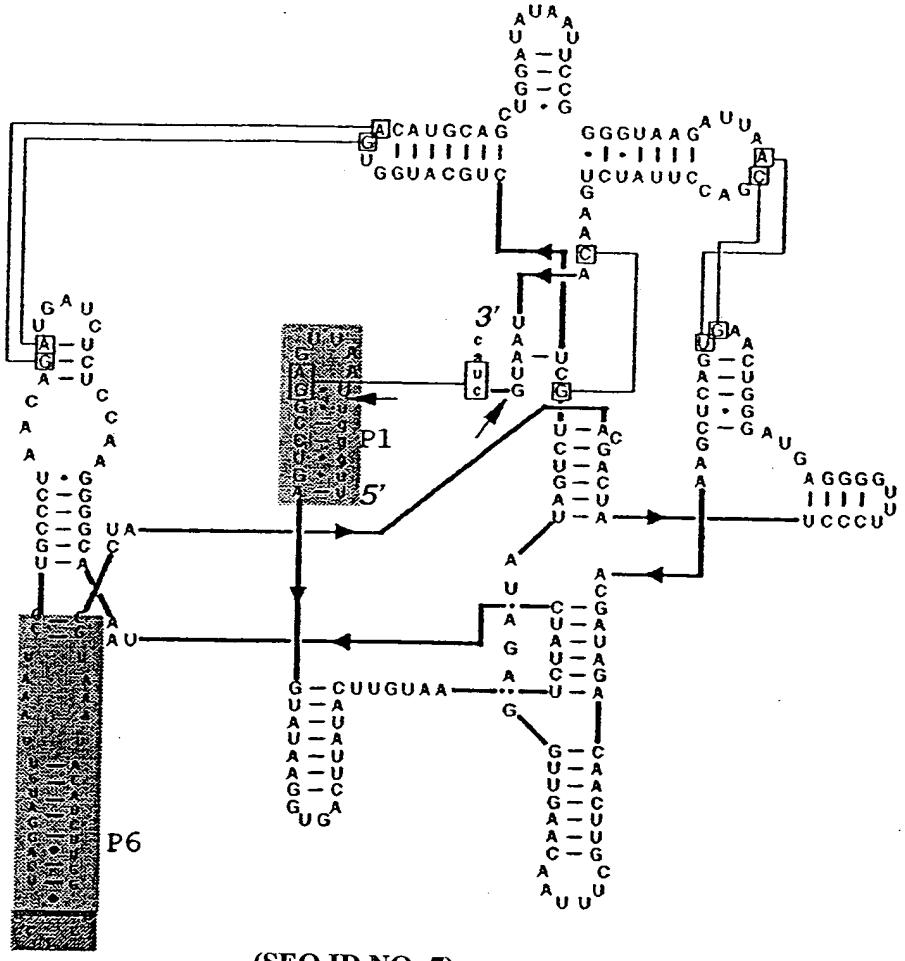

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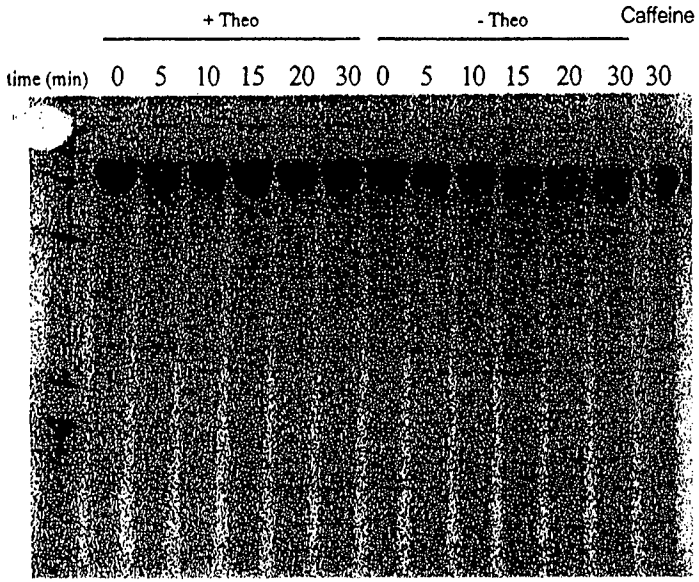
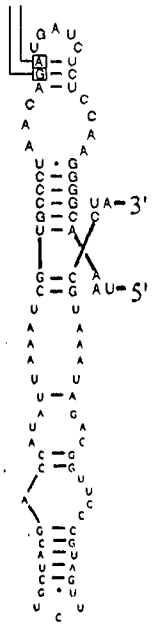
Figure 2a.





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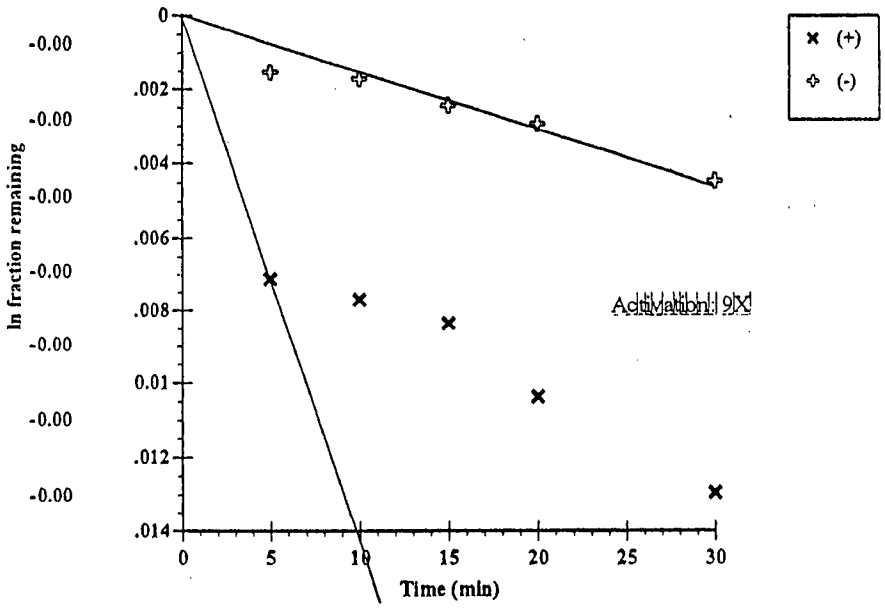
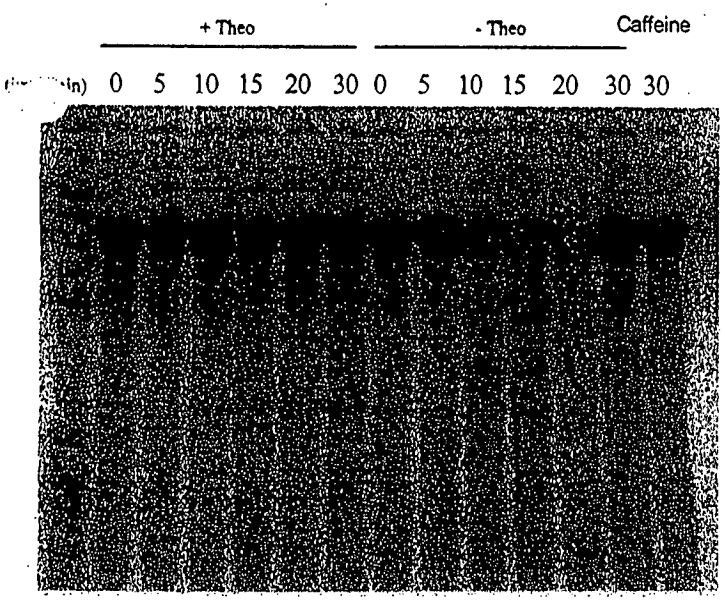
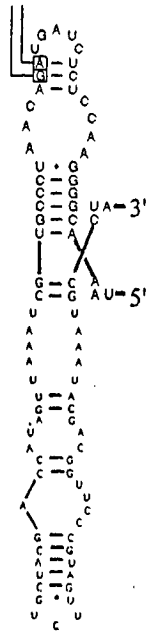


Figure 2b.





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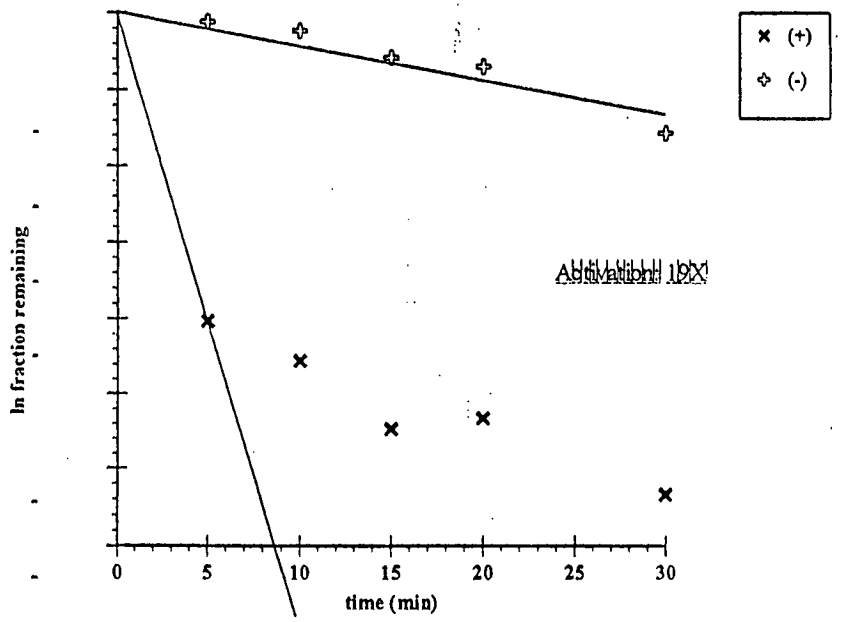

Figure 3.

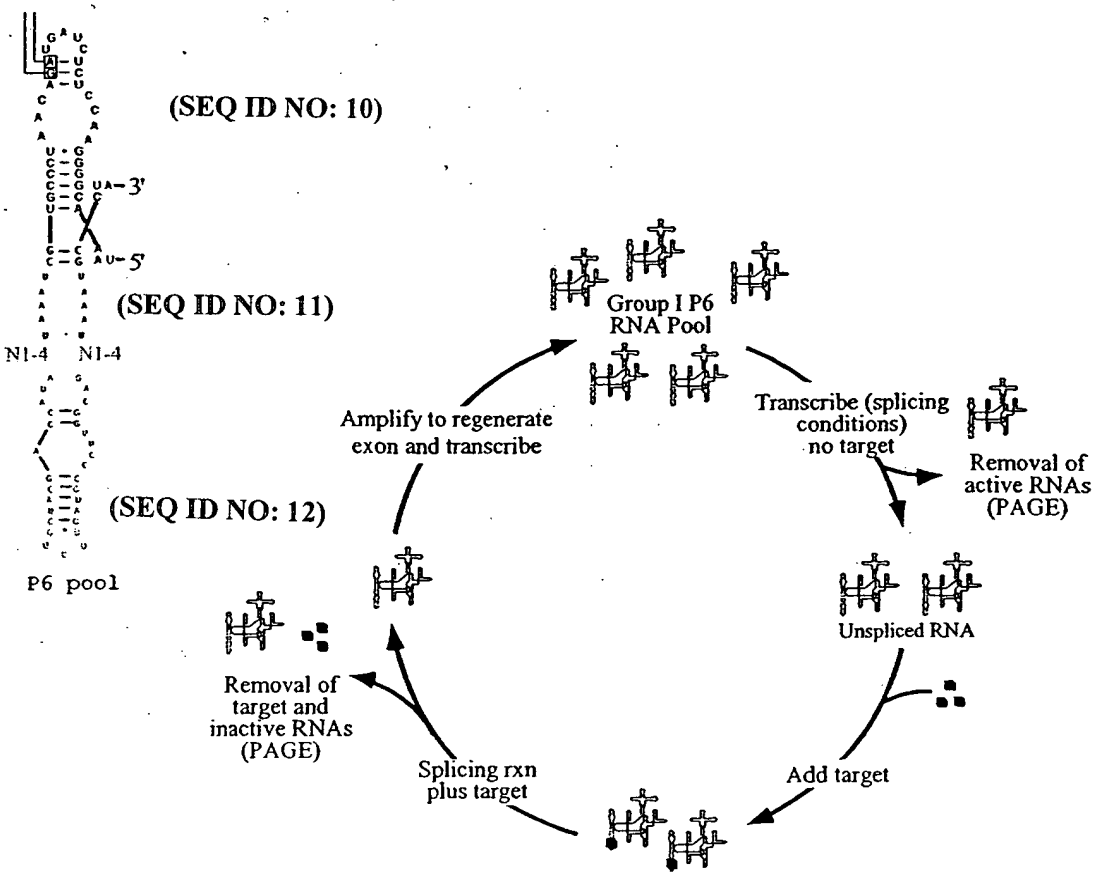

Figure 1.

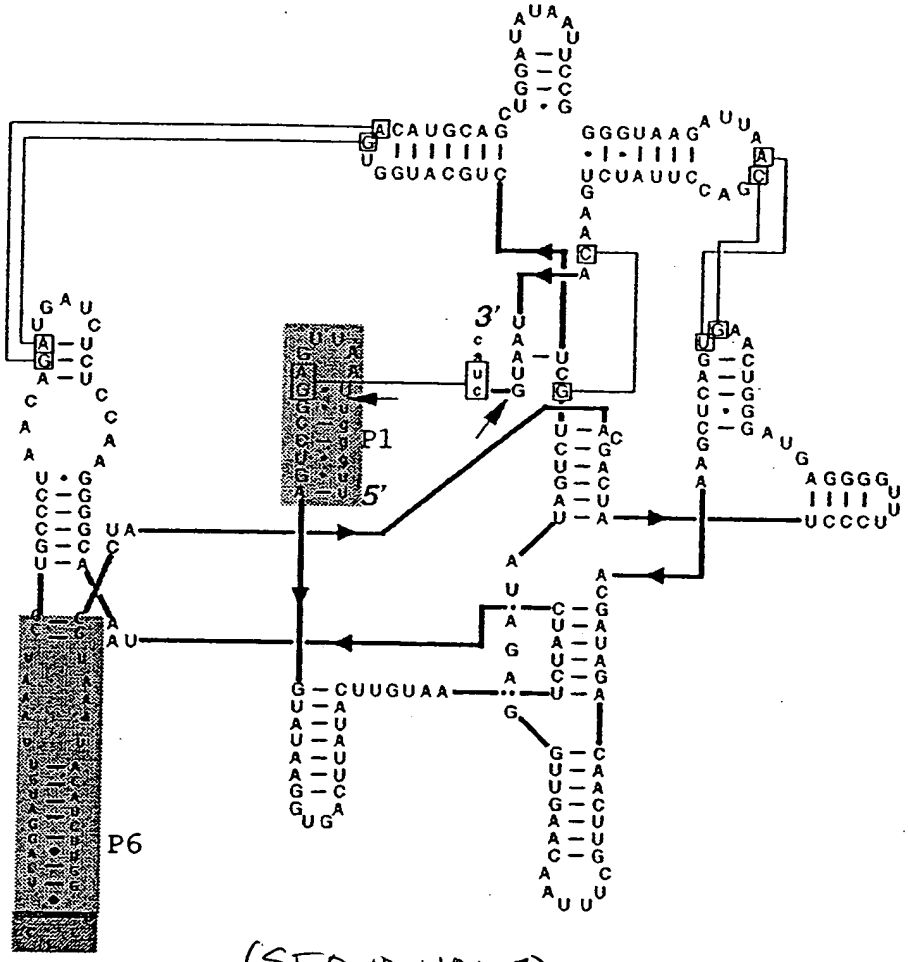

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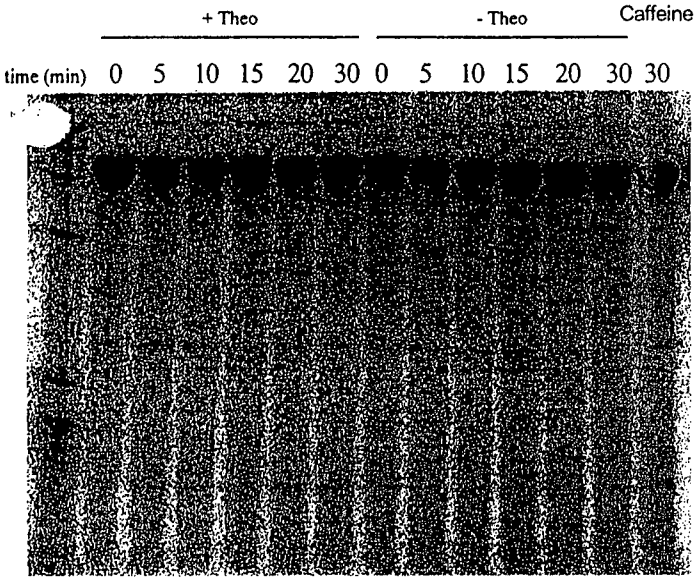
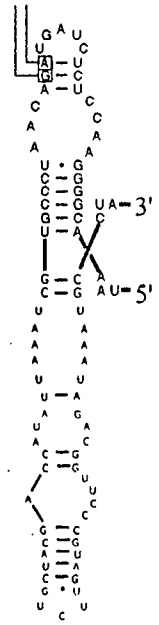
Figure 2a.





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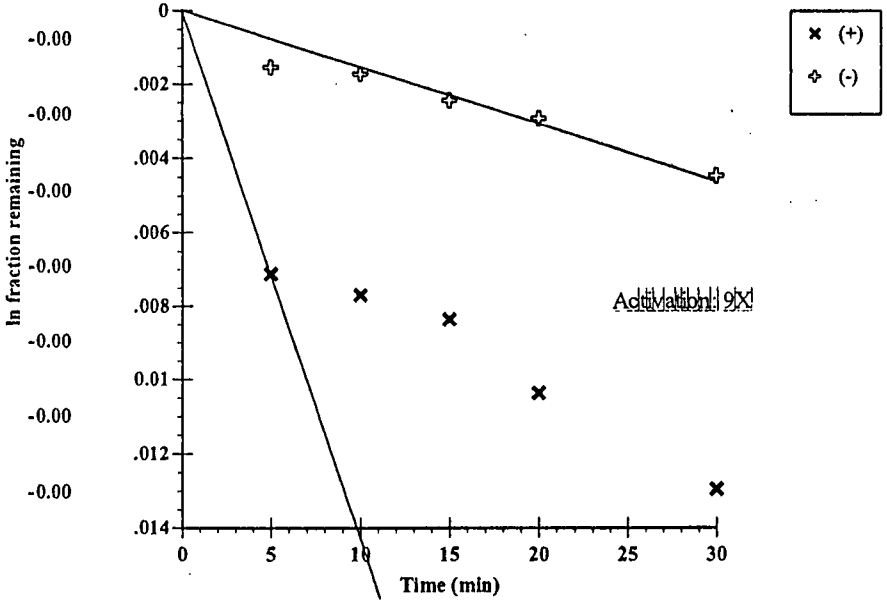

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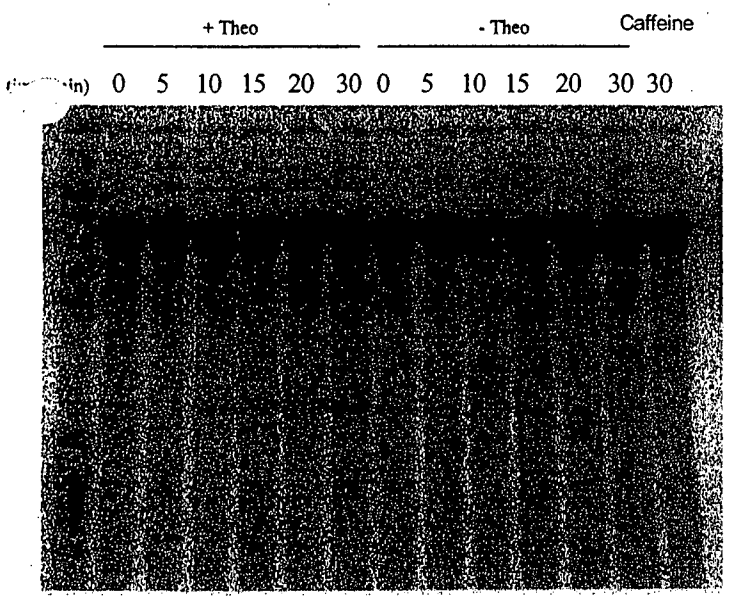

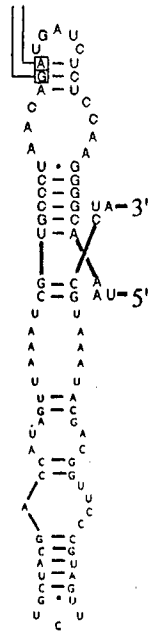

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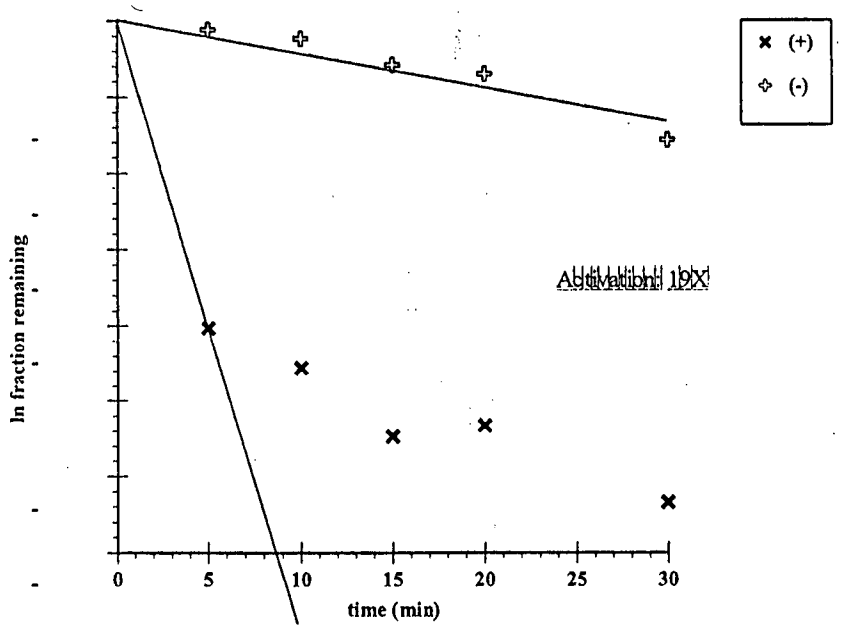

Figure 3.